REMARKS

The undersigned thanks the Examiner for the courtesies extended in the telephone discussion on June 30, 1997 regarding 35 U.S.C. §112, first paragraph objections and rejections, the substance of which is set forth below.

Claims 1-7, 10, 22-28, and 34-38 are pending in the above-identified application. Claims 2, 22, 24, and 36 are amended in view of the 112 rejections. Claims 39-48 are newly added. Support for the amendments to the claims and the newly added claims may be found in the specification as filed; in regard to delayed type hypersensitivity response, see for example page 18, lines 9, page 20, lines 1-28, page 22, lines 9-10 and 27, page 28, line 10, page 33, lines 20-28, and page 34, lines 1-10; in regard to T cell infiltration, see for example, page 31, line 9 and page 43, line 13; in regard to inflammatory immune response, see for example, page 17, lines 6, 13, and 14, page 18, line 8, page 21, line 26, and page 23, line 1; in regard to the presence of whole and disrupted cells in claims 45 and 46, it is apparent from and a necessary result of the procedure on page 16, lines 1-5; in regard to the administration of the vaccine at least six times, support can be found in Examples 5 and 6 and in the specification on page 29, lines 2-3, in regard to tumor regression and prolongation of survival, support can be found in Examples 4, 5, and 6 and in the specification on page 17, lines 6 and 10. No new matter is added. The newly added claims are considered together with the pending claims in response to the outstanding rejections. Claims 1-7, 10, 22-28, and 34-38 are rejected pursuant to 35 U.S.C.

§112, first paragraph, second paragraph, 102(a), and 103, and the specification is objected to pursuant to 35 U.S.C. §112, first paragraph.

OBJECTIONS AND REJECTIONS PURSUANT TO 35 U.S.C. §112 FIRST PARAGRAPH

The specification is objected to and claims 1-7, 10, 22-28, and 34-38 are rejected under 35 U.S.C. §112, first paragraph as failing to enable a skilled artisan to use a pharmaceutical composition comprising a hapten-modified tumor cell for treating various cancers. The Examiner states that the specification teaches a melanoma vaccine but fails to teach how to select tumor cells which would be effective in treating other cancers. Applicant respectfully traverses this rejection.

The specification as filed provides ample guidance how to isolate tumor cells, conjugate them to hapten and prepare and administer a vaccine containing such hapten-modified tumor cells. *See*, for example, page 15, lines 25-28, and page 16, lines 1-13, and Examples 4, 5, and 6. The Examiner in fact does not question the adequacy of this disclosure but appears to doubt that vaccines prepared and administered according to the present disclosure would be effective to treat cancers other than melanomas. In other words, the Examiner doubts that vaccines made in the same manner but comprising tumor cells from tumors other than melanoma would be effective.

Applicant's counsel has previously submitted a Declaration by the inventor, Dr. David Berd, attesting that one skilled in the art would expect that a vaccine prepared and used as

described in the specification would be effective for treating not only melanomas but also other tumors. *See* pages 10-13 of the Berd Declaration submitted together with the Response dated November 21, 1996. The Examiner, however, does not find Dr. Berd's statements persuasive primarily in view of the teachings of Bystryn , JC, "Tumor Vaccines", *Cancer Metastasis Rev.*, *9*(1):81-91, 1990. The undersigned notes for the record that the publication date of the Bystryn reference is July, 1990. The filing date of parent application 520,649 is May 8, 1990. Provided herewith is a citation and abstract for the Bystryn reference. Nonetheless, the remarks below address the Bystryn reference.

The Examiner believes that Dr. Berd's statements are contrary to the teaching of Bystryn that in order to achieve an effective cancer immunotherapy the induced immune responses must be directed to antigens expressed by the cancer being treated. However, Bystryn teaches that (i) cancer antigens vary among individuals for cancers of the same histological type; (ii) a profile of tumor antigens may be altered during the progression of a tumor and (iii) a profile of tumor antigens may be expressed by different cells of the same histological type in the same individual. Based on this, Bystryn concludes that (A) vaccines prepared from a single tumor antigen will not be effective against a broad range of tumors and (B) even autologous vaccines may not be effective against other tumor cells in the same patient.

It is submitted that point (i) and conclusion (A) of the Bystryn reference are irrelevant to the vaccine and method of treatment of the present invention, because the vaccine is prepared using *syngeneic* cancer cell that are not intended for use in individuals having different genetic

background. The present claims do not call for a vaccine and method of treating various cancers using *one* cancer antigen, but rather tumor cells which comprise a greater number of antigens. Moreover, the tumor cells of the present invention have been *haptenized* which increases the immune response to them. Bystryn teaches no haptenization.

It is not clear how points (ii) and (iii), and conclusion (B), of the Bystryn reference show that a vaccine and method of treatment of the present invention would not be expected to work. The present invention is directed to a composition and method which comprises a human tumor cell of the same type as the malignant tumor of which the patient is suffering.

It is also unclear how points (ii) and (iii), and conclusion (B), of the Bystryn reference show that a vaccine and method of treatment of the present invention would not be expected to work with cancers other than melanoma. If anything, these points and the conclusion suggest that an effective vaccine using autologous cancer cells cannot be made for *any* type of cancer. In other words, according to Bystryn, not even a melanoma vaccine using autologous melanoma cancer cells could be effective. This is clearly contrary to the results presented in the present specification (see Examples of the subject specification). In fact, the Examiner concedes that the specification teaches an effective melanoma vaccine.

The Examiner does not provide other reasons as to why the vaccine and method of the present invention would not be effective for all cancers. Reliance on the Hellstrom reference is not warranted because Hellstrom teaches that *allogeneic* tumor cells are not effective

immunogens. Claims of the present application call for a vaccine and a method of treating using *syngeneic* tumor cells.

More important, the Examiner fails to take into consideration that the vaccine of the invention is made effective due to the presence of a hapten modified tumor cell. Results in Example 6 clearly show that a vaccine containing hapten-conjugated tumor cells is effective while the vaccine containing the same type of cells without hapten is not. Accordingly, the hapten plays a key role in inducing an immune response against the tumor. Therefore, the immune response elicited by the melanoma vaccine of the invention is not due to the fact that the tumor happened to be melanoma. The present specification clearly teaches that syngeneic tumor cells isolated from any type of tumor (e.g. ovarian, lung, leukemia) would be conjugated to a hapten before administered as a vaccine. There is no reason to expect that hapten would help induce immune response to a melanoma tumor but not to other tumors.

To the contrary, because the immune system recognizes haptenized tumor cells, a person of ordinary skill would reasonably expect the invention to be operable for any tumor type.

Additionally, protocols for a vaccine containing haptenized 1) leukemia cells, 2) advanced ovarian cancer, and 3) liver metastases of adenocarcinoma of the colon have been approved for a clinical trial by the Institutional Review Board of the Thomas Jefferson University, the assignee of the present application. The members of this board who gave such approval are at least of ordinary skill in the field. They clearly expect the vaccine to work or they would not have approved the studies. The three protocols are provided herewith.

Furthermore, a clinical trial that will include 40 ovarian carcinoma patients has already begun at the same institution. After just a few weeks of treatment six of six patients have developed strong DTH responses to haptenized tumor cells. The ovarian protocol is also provided herewith.

These are very encouraging results and bolster the expectation of success of vaccines for the treatment of other cancer types.

It is respectfully submitted that if the vaccine of the present invention works for morphologically distinct types of cancer such as, for example, leukemia, ovarian cancer and melanoma, it will also work for all other types of cancer.

With respect to the rejection outlined at page 5, paragraph 3, to page 7, paragraph 2, of the April 7, 1995 Office Action, the teachings of Rotzschke *et al.* are believed irrelevant since the present claims do not call for a composition comprising tumor cells extracts.

The specification is further objected to, and claims 2-7, 10, 22-28, and 34-38, are rejected, under 35 U.S.C. 112, first paragraph, as failing to provide guidance to use the composition of the above claims with *any* adjuvant. The Examiner states that adding a particular adjuvant, *i.e.*, Bacille Calmette-Guerin ("BCG") may be critical. Applicant respectfully traverses this rejection.

The present invention is directed to a composition comprising a hapten modified human tumor cell having the property when administered with an adjuvant to a human suffering from a malignant tumor of the same type as said tumor cell, of eliciting 1) a delayed-type

hypersensitivity response, 2) an inflammatory immune response, or 3) eliciting T lymphocytes that infiltrate the tumor of said human, and a method of using the composition to treat cancer.

It is submitted that use of immunological adjuvants other than BCG is both enabled and described. See specification page 6, lines 26-27 and page 14, lines 7-8 and 15-17. Further supporting the specification is the Declaration of Dr. David Berd dated November 21, 1996, see page 10, paragraph 4.2. Dr. Berd's Declaration addresses the use of different types of adjuvants in combination with the composition of the present invention. Applicant has tested BCG as a representative of adjuvants in general and Dr. Berd identifies adjuvant equivalents of BCG, including QS-21 comprising a homogeneous saponin purified from the bark of *Quillaja saponaria*, *Corynebacterium parvum*, another adjuvant from a bacterial source, and IL-12. There is no basis for requiring restriction to a particular adjuvant. There is no evidence that the invention will not be operable if any other adjuvant is used. Naturally, use of adjuvant may be subject to optimization. But such optimization is well within the skill of the art.

The Examiner appears to rely on a statement in the specification bridging pp. 27-28 that all vaccines were mixed with BCG. However, this statement refers to the particular vaccines used in treating patients in working Example 4 and does not limit the scope of the invention.

The Examiner further states that the specification does not provide guidance for using a composition in which the melanoma cells are not "irradiated." In response, the claims have been written or amended to recite that tumor cells are "substantially in a no growth phase." Support for this amendment is found in the specification as filed, at page 12, lines 18-22. No new

matter is added. Applicant respectfully requests reconsideration and withdrawal of this rejection.

Turning to the type of tumor cells used in the present invention, the claims are amended above such that the human tumor cells are syngeneic. No new matter is added. Syngeneic refers to tumor cells that are genetically identical, especially with respect to antigens or immunological reactions, see Webster's Ninth New Collegiate Dictionary, Merriam-Webster Inc., Springfield MA, 1986, copy provided herewith. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

The Examiner further states that the specification does not provide guidance for using a composition of the invention with *any* hapten. Applicant refers to the specification as filed, page 15, lines 3-11, in support of haptens, in general. Representative examples of haptens disclosed in the specification are dinitrophenyl, trinitrophenyl, and N-iodoacetyl-N'-(5 sulfonic 1-naphtyl) ethylene diamine, see page 15, lines 6-8. Indeed, any small chemical entity that does not alone induce an immune response may function as a hapten.

Furthermore, the Declaration of Dr. David Berd dated November 21, 1996, page 9, paragraph 4.1, states that a number of chemically diverse compounds may be employed as haptens for use in the present invention, including and not limited to trinitrobenzenesulfonic acid, fluorescein isothiocyanate, arsenic acid benzene isothiocyanate, trinitrobenzenesulfonic acid, and dinitrobenzene-S-mustard (Nahas and Leskowitz, *Cellular Immunol.* **1980** *54*:241, reference "BR" of Supplemental Information Disclosure Statement dated November 21, 1996). Nahas and

Leskowitz identify a number of hapten linkages to tumor and spleen cells, including azobenzenearsonate (ABA), arsonic acid benzene isothiocyanate (AB-NCS), trinitrobenzenesulfonic acid (TNBS), dinitrobenzenesulfonic acid (DNBS), dinitrobenezeneazo (DNBA), dinitrobenzene-S-mustard (DNBM), and fluorescein isothiocyanate (Fl-NCS). Nahas and Leskowitz identify success in coupling chemicals to the cells *in vitro* via ϵ-amino groups or -COOH groups. Another report by Sherman *et al.* is identified by Nahas and Leskowitz, see page 245-246, as successful in generating ABA coupled target cells *in vivo*.

Accordingly, in view of the remarks set forth above and the amendments to the claims, Applicant respectfully requests reconsideration and withdrawal of the 112, first paragraph objection and rejections.

REJECTION PURSUANT TO 35 U.S.C. §112 SECOND PARAGRAPH

Claims 2-7, 10, 22-28, and 34-38 are rejected under 35 U.S.C. §112 second paragraph as indefinite.

A.) Claim 2 is alleged to be indefinite for lack of antecedent basis for the language "said tumor." Claim 2 is amended above to refer to "said tumor cell" of claim 36. Accordingly, Applicant respectfully requests withdrawal of the rejection of claim 2.

B.) Claim 4 is said to be indefinite. Claim 4 is canceled above. Thus, Applicant respectfully requests withdrawal of the rejection of claim 4.

C.) Claims 22-28, 34, 35, and 38 are alleged to be indefinite as being drawn to a composition comprising a hapten modified human tumor cell. Claim 2 was recommended to include an acceptable carrier. This rejection is repeated for composition claims 2-7, 10, 36, and 37 in the Office Action dated February 4, 1997, page 7, lines 9-14. These rejections are considered together. While the above-identified Office Action identifies claim 36 as being drawn to a composition, it is respectfully noted that claim 36 is drawn to a method.

A claim may be considered indefinite if its scope takes on an unreasonable degree of uncertainty when construed in light of the application disclosure and what is known in the art. *In re Cormany*, 177 USPQ 450 (CCPA 1973). However, within the confines of §112, Congress intended that Applicants be provided considerable latitude in their choice of claim form and language. *In re Duva*, 156 USPQ 90 (CCPA 1967).

Applicants are permitted to define their own invention with a reasonable degree of particularity and distinctness and latitude in the manner of expression. See *In re Gay*, 135 USPQ 311 (CCPA 1962) and M.P.E.P. §§608.01(O) and 706.03(d).

The composition of the present invention comprises a haptenized human tumor cell, which cell has the property, when administered with an adjuvant to a human suffering from a malignant tumor of the same type as the tumor cell, of eliciting T lymphocytes that infiltrate the tumor of the human subject. In addition a composition may elicit an inflammatory immune response or a delayed-type hypersensitivity response to the tumor of a human subject. In the absence of a statutory requirement or rule that requires a composition to include more than one

ingredient, the claims particularly point out and distinctly claim the subject matter of the present invention and are in accordance with 112, first paragraph. The claimed compositions are useful as vaccine components and may be manufactured separately from any other ingredient that may be incorporated in a vaccine. Applicant respectfully requests reconsideration and withdrawal of this rejection.

D.) Claims 22-28, 34, 35, and 38 are said to be indefinite in view of the recitation "a hapten modified human tumor cell." The claim is alleged to be confusing because it does not recite how the cell is modified. This rejection is repeated for composition claims 2-7, 10, 36, and 37 in the Office Action dated February 4, 1997, page 7, lines 15-18. These rejections are considered together.

Applicant has defined the invention in a manner known to him at the time the invention was made. While not intending to be bound by any particular theory of operation, a cell useful in the present invention is haptenized. The effect of hapten modification is to increase immune response to the cell. Nonetheless, the claims are amended according to specification p. 15, lines 4-6 (see also p. 33, lines 6-18). Additionally the present claims recite the effect achieved with the haptenized human tumor cells, i.e. delayed type hypersensitivity response, T cell infiltration, or inflammatory immune response against the tumor. Accordingly, administration of cells haptenized in accordance with the present invention results in three responses which particularly points out and distinctly claims the subject matter of the present invention. Thus, Applicant respectfully requests reconsideration and withdrawal of this rejection.

E.) Claim 23 is said to be indefinite. Claim 23 is canceled above. Thus, Applicant respectfully requests withdrawal of the rejection of claim 23.

F.) Claim 24 is alleged to be indefinite for lack of antecedent basis for the language "said tumor." Claim 24 is amended above to refer to "said tumor cell" of claim 22. Accordingly, Applicant respectfully requests withdrawal of the rejection of claim 24.

G.) Claim 25 [*sic* and 25] is alleged to be indefinite for lack of antecedent basis for the language "said tumor." Claim 25 is amended above to refer to "said tumor cell" of claim 22. Accordingly, Applicant respectfully requests withdrawal of the rejection of claim 25.

In view of the forgoing amendments and remarks, Applicant respectfully requests reconsideration and withdrawal of the 112, second paragraph rejections of the claims.

THE PRESENT INVENTION

The present invention is directed to compositions comprising a haptenized human tumor cell, which cell has the property, when administered with an adjuvant to a human suffering from a malignant tumor of the same type as the tumor cell, of eliciting activated T lymphocytes that infiltrate the tumor of the human subject. Another embodiment of the present invention is directed to such a composition which elicits an inflammatory immune response against the tumor of a human subject. Yet another embodiment of the present invention is directed to compositions that elicit a delayed-type hypersensitivity response to the tumor of a human subject.

Methods of the present invention include a method of eliciting T lymphocytes to infiltrate a tumor of a patient comprising administering to the patient a composition comprising a therapeutically effective amount of a haptenized human tumor cell and an adjuvant wherein the patient suffers from a malignant tumor of the same type as the tumor cell, and measuring T lymphocytes that infiltrate the patient tumor. In addition, methods of eliciting an inflammatory immune response to a tumor of a patient and a method of eliciting a delayed-type hypersensitivity response to a tumor of a patient are also encompassed by the present invention.

REJECTION PURSUANT TO 35 U.S.C. §102(a)

Claims 2-7, 10, 22-28, and 36-38 are rejected under 35 U.S.C. §102(a) as unpatentable over Murphy *et al.*, *Lab. Investigation*, **1990** *62*(1)70A, hereinafter "Murphy *et al.*"

The present claims are supported by the disclosure of U.S. patent application Serial No. 07/520,649, filed May 8, 1990, now abandoned. A Declaration of Dr. David Berd, inventor of the above-identified subject matter, is attached hereto. Dr. Berd attests to the involvement of each of the co-authors of the Murphy *et al.* reference and verifies that the involvement of each of the co-authors does not amount to inventorship. Indeed, the role of the co-authors is as follows:

Dr. George F. Murphy was consulted on the pathology of the patient tumor samples, reading slides of biopsy sections to characterize tumor inflammation. Antoneta Radu was an assistant of Dr. Murphy and also read slides of biopsy sections under Dr. Murphy's direction.

Dr. Michael Mastrangelo provided patient tumor samples and assisted in the clinical care of the patients. Dr. Berd's Declaration provides a satisfactory showing that would lead to a reasonable conclusion that he (and not his co-workers) is the inventor of the subject matter disclosed in the article and the claimed in the application. *In re Katz*, 215 USPQ 14, 18 (CCPA 1982). Accordingly, in view of the Declaration of Dr. Berd, the support for the present invention in the 07/520,649 application, and the remarks set forth above, the rejection under 35 U.S.C. §102(a) should be withdrawn.

Claims 2-7, 22-28, and 34-38 are rejected under 35 U.S.C. §102(a) as anticipated by Berd *et al.*, *Proc Am Assoc Cancer Res Annu Meet* [**1989** *sic* 1990] *30*:382, hereinafter "Berd *et al.*"

The Office Action dated February 4, 1997 refers to the Berd *et al.* reference previously cited in the Office Action dated April 7, 1995, page 11. Since two Berd *et al.* references are discussed on page 11 of the April 7, 1995 Office Action, a telephone call to the Examiner clarified this reference as the Berd *et al.* reference cited in the 102(a) rejection of the April 7, 1995 Office Action. The proper citation of the reference is set forth above in the preceding paragraph.

The first sentence of Berd *et al.* (1989) refers to knowledge in the art *prior* to the work summarized in the Berd *et al.* abstract. The first sentence of Berd *et al.* is identical to discussion of prior art on p. 5, lines 7-15 of the specification.

Indeed it had been tried prior to the Berd *et al.* abstract and prior to the present invention that DTH responses had been observed in melanoma patients inoculated with autologous melanoma cells after receiving low-dose cyclophosphamide and that in some cases metastatic tumors had regressed. However, as indicated in the specification, and as suggested by Berd *et al.* in the second sentence, there was a need in the art at the time of Berd *et al.* and at the time of the present invention to increase the efficiency of vaccines containing melanoma cells. The authors of Berd *et al.* characterized their new work as an attempt to increase efficiency of a vaccine containing melanoma cells.

It is submitted that the 1989 abstract does not suggest that preparation involving haptenized melanoma cells would be as good as prior preparations, let alone better than prior preparations. Thus, the Berd *et al.* abstract discloses insufficient information. The abstract does not suggest that an efficacious vaccine can be produced by using autologous melanoma cells conjugated to a hapten. The reported study involved only four patients with metastatic melanoma which were injected with DNP-conjugated melanoma cells. No comparative data using a vaccine with non-DNP melanoma cells were presented. Thus, the observations regarding the tumors cannot be attributed to the vaccine. Accordingly, one skilled in the art would not have been able to determine, in the absence of any teaching or suggestion in the Berd *et al.* abstract, if DNP modification increase efficacy of the vaccine.

There would not have been any reasonable expectation that a vaccine as efficient as the one described in the present application can be produced. To the contrary, one skilled in the

art could have reasonably concluded that the results of the Berd *et al.* abstract are attributable to the presence of melanoma cells and not to the presence of DNP. Nothing in the Berd *et al.* abstract makes it more likely than not that a DNP-conjugated melanoma vaccine would be more effective than an unconjugated melanoma cell vaccine.

Furthermore, the results presented by Berd *et al.* do not suggest an efficacious vaccine of the present invention. Only one of the tested patients developed erythema (an indicator of vaccine efficacy) in the dermal metastases themselves. This does not suggest an effective treatment for melanoma. Two patients developed erythema in the skin overlying the metastases (at the time of publication, suggesting an irrelevant immune response), and one patient had no response. There was no evidence that erythema in the skin overlying the metastases in two patients extended to the tumor. It was only subsequently observed that erythema in the skin overlying the metastases reflected a tumor inflammatory response.

In contrast, the vaccine and treatment of the present invention causes an unexpectedly higher immunity directed at the tumor. The immunity observed in Berd *et al.* (1989) can be said to be directed to the hapten or at the skin but not at the tumor. For example, as disclosed in Example 4, (page 30, lines 23-27) the ability of a vaccine comprising DNP-modified melanoma cells to prolong disease-free survival and total survival in treated patients is significantly higher ($p < 0.01$) than the same ability of a vaccine comprising non-conjugated melanoma cells. Example 6 of the present specification shows that hapten-modified melanoma cells can increase total survival rate from 27% to 59% (page 42, lines 1-5). The Berd *et al.* abstract neither

discloses nor suggests that using DNP-conjugated cells would result in such an efficacious vaccine or treatment. Without such a suggestion, one skilled in the art would not have had a reasonable expectation of success that a vaccine described and claimed in this application can be produced by using the method described in the present specification or that use of such a vaccine would be an effective treatment.

In summary, the Berd *et al.* does not disclose a composition that is effective as a vaccine against melanoma or that would be considered promising (let alone more promising than the prior art at that time) as a vaccine against melanoma. Similarly Berd does not disclose a method for eliciting immune response against melanoma tumor much less a therapeutic immune response. There is no teaching much less suggestion in the Berd abstract of an immune response observed in melanoma patients as a result of the treatment. There is no teaching or suggestion of an inflammatory immune response or of eliciting activated T lymphocytes to the tumor. Certainly, Berd *et al.* does not disclose or suggest any vaccine for any other type of cancer and does not suggest a method for treating any other type of cancer. Finally, Berd *et al.* does not disclose or suggest administration of more than two doses of a vaccine against melanoma.

In view of the foregoing remarks and *In re Katz*-type Declaration of Dr. David Berd, Applicant respectfully requests reconsideration and withdrawal of the 102(a) rejections.

REJECTION PURSUANT TO 35 U.S.C. §103

Claims 2-7, 10, 22-28, and 36-38 are rejected under 35 U.S.C. §103 as unpatentable over Berd *et al.* or Murphy *et al.*, in view of Geczy *et al.* Applicants respectfully traverse this rejection.

The Murphy *et al.* reference is removed as a proper prior art reference in view of the remarks set forth above and the *In re Katz*-type Declaration of Dr. David Berd, filed herewith. The Geczy reference standing alone does not teach or suggest the vaccine and methods of treatment of the present invention. The Examiner cites this reference merely to assert that the dinitrochlorobenzene (DNCB) used by Murphy to sensitize patients before vaccine administration is interchangeable with 1-fluoro-2,4-dinitrochlorobenzene which has been used as a sensitizing agent by the present inventor. Accordingly, withdrawal of the rejection under 35 U.S.C. § 103 over Murphy in view of Geczy is believed to be in order and is respectfully requested.

With respect to the rejection of claims 2-7, 10, 22-28, and 36-38 as obvious over Berd *et al.* (1989) in view of Geczy *et al.*, it is believed that the combined teachings of the cited references fail to suggest the composition and methods of the present invention. As discussed in detail under the "Rejection Pursuant to 35 U.S.C. § 102(a)", the Berd (1989) abstract fails to teach or suggest an effective vaccine or methods of treatment of various tumors using syngeneic hapten-modified tumor cells. In summary, the Berd abstract fails to suggest that an effective vaccine can be produced by administering hapten-modified tumor cells because (i) in the absence of control experiments one skilled in the art would not have known if DNP-

conjugated melanoma vaccine is equally, more, or less effective than the unconjugated melanoma vaccine, and (ii) based on the results presented in the Berd abstract (*i.e.*, only one patient showed changes in the tumor itself) one skilled in the art would not have reasonably expected that a vaccine and a method of cancer treatment as effective as the one described and claimed here can be achieved.

The Geczy reference does not provide further expectation of success even if combined with the teachings of the 1989 Berd abstract. As noted above, this reference was cited for its limited teaching that dinitrochlorobenzene (DNCB) and 1-fluoro-2,4-dinitrochlorobenzene may be interchangeable. Accordingly, the obviousness rejection over Berd (1989) in view of Geczy should be withdrawn.

In view of the remarks set forth above, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §103.

CONCLUSION

In view of the foregoing amendments in response to 112, first and second paragraphs, remarks, Webster's Ninth New Collegiate Dictionary definition of "syngeneic," and Dr. Berd's

In re Katz Declaration, Applicant respectfully requests reconsideration and allowance of all pending claims. Early and favorable notification of the same is earnestly solicited.

Respectfully submitted,

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